coated non-liposomal formulations." Indeed, all of the independent claims in the present application recite "non-liposomal pharmaceutical formulations." One skilled in the art would understand that non-liposomal formulations have the ability to form liposomes but are themselves *not* liposomes. As such, the formulations of Claims 8, 13-23 and 35 have "the ability to generate suspension or liquid forms of the formulation." (Specification, page 6, line 30). Therefore, the terms liquid and suspension are definite with respect to the current invention. Accordingly, Applicant respectfully requests withdrawal of the § 112, second paragraph, rejection of Claims 8, 13-23 and 35.

Provisional Rejection for Double Patenting

The Examiner provisionally rejected Claims 1-12 and 37-38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 14-39 and 41-60 of co-pending Application No. 09/562,207. However, "[u]nless a claimed invention in the application is obvious over a claimed invention in the patent [in this case, Application No. 09/562,207], no double patenting rejection of the obviousness-type should be made." M.P.E.P. §804 ¶ II.B.1(a).

Claims 1-12 and 37-38 of the current application are patentably distinct from the claimed invention in Application No. 09/562,207. Claims 1-12 and 37-38 of the current application are directed to *a non-liposomal* pharmaceutical formulation. Indeed, all of Applicant's claims explicitly recite "a non-liposomal pharmaceutical formulation." By contrast, Claims 14-39 and 41-60 of Application No. 09/562,207 are all directed to *proliopsomal* preparations. Thus, as further discussed below, Applicant's claimed invention is completely novel, non-overlapping and non-obvious over the claimed invention in Application No. 09/562,207. Accordingly, Applicant respectfully asserts that the Examiner withdraw the rejection under the judicially created doctrine of obviousness-type double patenting.

1. Applicant's non-liposomal claims and the cited proliposomal claims in Application No. 09/562,207 do not overlap in scope.

Applicant's claims to non-liposomal formulations and the cited proliposomal claims are not only patentably distinct, but are also completely non-overlapping. The cited application, Application No. 09/562,207 (not commonly owned with the current application) represents Applicant's prior work in the field. As disclosed in Applicant's current specification, Applicant's prior patent application describes a liposomal method for delivering drugs in which

the drug *is* exposed to an aqueous phase, whereas Applicant's current application is directed to a non-liposomal formulation which is *not* exposed to an aqueous phase.

Application No. 09/562,207 explicitly discloses the use of liposomes in the preparation of proliposomal preparations. Liposomes, as known in the art and as defined in Application No. 09/562,207, comprise "an enclosed lipid droplet having a core, typically an aqueous core, containing the compound." (Application No. 09/562,207, page 2, lines 8-10). Thus, the claimed invention in Application No. 09/562,207 is directed to a proliposomal preparation which is derived from a liposomal (and thus aqueous) preparation.

Application No. 09/562,207 specifically discloses its use of liposomes, and thus, its use of an aqueous phase:

- [T]he invention relates to *liposomes* and formulations of drugs, nutrients and other compounds into *liposomes* (Application No. 09/562,207, page 1, lines 7-8. Emphasis added).
- These results demonstrated that *liposomes* can be successfully prepared for oral administration in the form of enteric-coated proliposomal tablets (Application No. 09/562,207, page 20, lines 20-21. Emphasis added).

By contrast, Claims 1-12 and 37-38 of the current application recite an invention in which the lipid and the drug are in a non-liposomal formulation. Applicant defines the term "non-liposomal" as "a formulation which is not exposed to an aqueous phase, and thus does not form liposomes, prior to the application of the enteric coating." (Specification, page 7, lines 12-21). Thus, unlike the invention recited in the claims of Application No. 09/562,207, the formulations of the current invention are *not* exposed to an aqueous phase.

Because Claims 1-12 and 37-38 of the current invention recite *non-liposomal* pharmaceutical formulations and because the claims of Application No. 09/562,207 all recite a *proliposomal* preparation, Claims 1-12 and 37-38 of the current application do not overlap with the cited claims and each set of claims is novel over the other. Moreover, as described below, the present invention is non-obvious over the invention claimed in Application No. 09/562,207.

2. *Applicant's Claims 1-12 and 37-38 are non-obvious over the cited claims in Application No. 09/562,207.*

There is no teaching or suggestion anywhere in the prior art to modify the proliposomal preparations in the claims of Application No. 09/562,207 into the non-liposomal formulations of the current invention. Indeed, there is no mention in the prior art that the aqueous phase used in

the preparation of the lioposomal/proliposomal formulations of Application No. 09/562,207 could or should be eliminated in order to protect water-labile drugs. One skilled in the art would not be motivated to modify the invention claimed in Application No. 09/562,207 to make or use the non-liposomal formulations of the present invention.

Further, Claims 1-12 and 37-38 of the current invention are particularly advantageous and provide unexpected results over the cited claims. As discussed above, in Applicant's claimed invention, there is no exposure to an aqueous phase. For water sensitive drugs and drugs that are labile in water, such as antibodies, the absence of an initial aqueous phase is particularly advantageous because the integrity of these drugs is preserved. (Specification, page 7, lines 15-18). Moreover, the cited claims in Application No. 09/562,207 all require "a protective coating in between the proliposomal preparation and the enteric coating." This express limitation of a protective coating is needed in Application No. 09/562,207 to prevent a drug from "swelling" upon exposure to an aqueous phase. Because the drugs of Applicant's current invention are non-liposomal and are not exposed to an aqueous phase, Applicant's current invention does not require this protective coating. Moreover, Applicant's current invention does not need to be a "calcium-free" composition, nor does it need to comprise an "aliphatic amine", as is recited in the proliposomal claims of Application No. 09/562,207. Thus, Claims 1-12 and 37-38 of the present application are directed to a non-obvious patentably distinct invention as compared to the cited claims.

In view of the above comments, Applicant respectfully asserts that Claims 1-12 and 37-38 of the present application are patentably distinct over the cited claims in Application No. 09/562,207. Accordingly, Applicant respectfully requests that the Examiner withdraw the provisional rejection for double patenting.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected Claims 1-38 under 35 U.S.C. §102(b) as anticipated by U.S. Pat. No. 5,206,219 to Desai. The Examiner states that "Desai discloses enteric formulations containing an active agent and a phospholipid and methods of making the preparation in the form of either capsules or tablets." Applicant submits that Desai merely discloses formulating a pre-emulsion solution consisting of a polyol solvent and a lipid solvent which can be encapsulated in a gelatin capsule. Desai does not teach or suggest a non-liposomal pharmaceutical formulation comprising at least one pharmaceutically active agent, at least one phospholipid and an enteric

coasting surrounding the pharmaceutically active agent and phospholipid, as recited in Applicant's Claim 1. Moreover, Desai dos not teach or suggest enteric coating of the phospholipid. Indeed, Desai teaches only encapsulating or packing a pre-emulsion solution into a capsule which has been coated with an enteric coating. (Desai, col. 5, lines 56-61). Thus, Applicant respectfully requests withdrawal of the § 102(b) rejection of independent Claim 1 and all claims which depend directly or indirectly therefrom, specifically Claims 2-12, 37 and 38.

With respect to Claims 13-36, Desai does not teach or suggest combining a pharmaceutically active agent with phospholipid to produce a combination, and then coating the combination with an enteric coating material to produce a coated product, as recited by Claim 13. Further, Desai does not teach or suggest combining at least one pharmaceutically active agent with at least one phospholipid in a non-aqueous solvent, evaporating the non-aqueous solvent, and applying an enteric coating material to the pharmaceutically active agent and the phospholipid, as recited by Claim 24. As stated above, Desai dos not even teach enteric coating of the phospholipid. Indeed, Desai only teaches encapsulating or packing a pre-emulsion solution into a capsule which has been coated with an enteric coating. (Desai, col. 5, lines 56-61). Thus, Applicant respectfully requests withdrawal of the § 102(b) rejection of independent Claims 13 and 24 and all claims which depend therefrom, specifically Claims 14-23 and 25-36.

In view of the above comments, Applicant respectfully requests that the Examiner withdraw the rejection of Claims 1-38 under § 102(b).

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected the Claims[1] under 35 U.S.C. § 103(a) as being unpatentable over Nakagame (U.S. Pat. No. 4,615,885) in view of Ganter (U.S. Pat. No. 5,635,206) by themselves or in combination.

The Examiner states that Nakagame discloses a "method of preparation of powders involv[ing] dissolving the phospholipid and evaporating the organic solvent [followed by addition of] aqueous medium containing active agent ... and lyophiliz[ing] to prepare proliposomal powder." Applicant respectfully asserts that Nakagame merely discloses a method of preparing lyophilized urokinase-carrying *liposomal* formulations, not the non-liposomal formulations of the current invention. The cited reference merely describes specialized delivery

[1] It is unclear which claims were rejected by the Examiner. To facilitate prosecution, Applicant will address all of the pending claims, Claims 1-38, in this application.

of urokinase to the intestinal tract in an absorbable form and discloses incorporating urokinase into the innerspace of liposomes. In preparing the liposome, phospholipids solutions are mixed with aqueous solutions of urokinase to give "an urokinase-carrying liposome." (Nakagame, col. 3, lines 4-14). With respect to Claims 1-12, 37 and 38 of the current application, Nakagame does not teach or even suggest a non-liposomal pharmaceutical formulation comprising at least one pharmaceutically active agent, at least one phospholipid and an enteric coating surrounding the pharmaceutically active agent and phospholipid, as recited in Claim 1. Moreover, Nakagame discloses forming a liposome only to carry the active agent. Specifically, Nakagame discloses solubilizing the active agent in an aqueous solution which is added to the phospholipid and thereby forms an active *agent-carrying* liposome. As such, Nakagame does not suggest preparing a non-liposomal formulation including phospholipids and therefore, Nakagame does not suggest and cannot suggest preparing a non-liposomal formulation with an enteric coating. Therefore, Nakagame by itself does not render Claims 1-12, 37 and 38 obvious.

The Examiner states that "Ganter while disclosing proliposomal compositions teaches that a mixture suitable for the preparation of liposomes can be made by mixing lecithin (phospholipid), solubilizer and/or lipophilic and hydrophilic active agents and preparing a dry powders without the addition of water." Ganter simply discloses preparing proliposomal formulations containing lecithin, lipophilic and/or hydrophilic compounds, 15-50% solubilizer and 0-10% water. (Ganter, col. 2, lines 38-47). Ganter states that the solubilizer can be polar organic solvents such as ethanol. (Ganter, col. 2, lines 12-14). Significantly, Ganter notes that the proliposomes "prepared by the process ... can be stored very easily [in part] because of their relatively high alcohol content." (Ganter, col. 2, lines 65-67).

While Ganter teaches preparation of proliposomes with 0-10% water, the proliposomes prepared contain significant amounts of solubilizer, *i.e.* 15-50%. As Ganter notes that the storage of the proliposomes is eased because of the "high alcohol content," the bulk of the solubilizer is retained in the Ganter proliposome formulation. Therefore, Ganter fails to teach or suggest preparation of a "dry powder" non-liposomal formulation. As such, Ganter does not and cannot suggest coating a "dry powder" non-liposomal formulation with enteric coating. Thus, Ganter by itself does not render Claims 1-12, 37 and 38 obvious. Therefore, neither Nakagame nor Ganter by themselves render Claims 1-12, 37 and 38 obvious.

For the same reasons, Nakagame and Ganter by themselves do not render the method claims (Claims 13-36) obvious. Again, Nakagame does not suggest creating a non-liposomal formulation, much less coating the non-liposomal formulation with an enteric coating. Similarly, Ganter does not suggest preparing a dry powder non-liposomal formulation nor does Ganter suggest coating a non-liposomal formulation (or a proliposomal preparation) with an enteric coating. As neither Nakagame or Ganter contains the teaching or suggestion to make the instant invention, neither Nakagame nor Ganter render Claims 13-36 obvious.

The Examiner states that "[o]mitting the step of the addition of an aqueous solution the dried phospholipid in Nakagame and prepare the dry powders would have been obvious to one of ordinary skill in the art since Ganter teaches the phospholipid mixtures could be prepared without the addition of water." However, Nakagame teaches away from omitting the step of the addition of water because forming the urokinase-carrying liposome is integral to the invention. One of skill in the art would understand that addition of water would be required to make the liposomes disclosed by Nakagame. Further, Nakagame notes that in the absence of liposome formation, "the efficiency of carrying the drug will be extremely low or impossible." (Nakagame, col. 4, lines 11-13). As such, omitting this step from Nakagame as the Examiner suggests would render the Nakagame invention unsatisfactory for its intended purpose. Moreover, due to the "high alcohol" content of the proliposomes produced by the Ganter process, the Ganter process does not teach or suggest preparation of a "dry powder" non-liposomal formulation but merely a proliposome formulation containing significant amounts solubilizer but no water. Accordingly, Nakagame in view of Ganter does not suggest and cannot suggest modification to achieve the instant invention. Therefore, neither Nakagame nor Ganter alone or in combination renders Claims 1-38 obvious. Thus, Applicant requests withdrawal of the § 103(a) rejection of Claims 1-38.

Reasons for Obtaining a One-Month Extension to Respond to the Office Action

Applicant gratefully acknowledges the grant of the Petition to Make Special in the above-captioned application. A Shortened Statutory Period to respond to the First Office Action was set to expire on September 24, 2002. Because Applicant was unable to obtain a copy of pending Application No. 09/562,207, which was cited by the Examiner under the judicially created doctrine of obviousness-type double patenting, until October 15, 2002, Applicant was forced to obtain a one-month extension in filing a response.

CONCLUSION

In view of the foregoing remarks, Applicant respectfully asserts that the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number indicated below.

No fees are believed to be due. However, please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 24 Oct. 2002

By: Daniel Altman

Daniel E. Altman
Registration No. 34,115
Attorney of Record
2040 Main Street
14th Floor
Irvine, CA 92614
(949) 760-0404

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